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Pharmacological studies of performance on the free-operant psychophysical procedure

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ABSTRACT

In the free-operant psychophysical procedure (FOPP), reinforcement is provided intermittently for responding on lever A in the first half and lever B in the second half of a trial. Temporal differentiation is measured from the psychometric function (percent responding on B, *%B*, versus time from trial onset, *t*), the index of timing being T_{50}, the value of *t* at *%B* = 50. T_{50} is reduced by acute treatment with 5-hydroxytryptamine (5-HT_{1A}, 5-HT_{2A}) and dopamine (D_1-like, D_2-like) receptor agonists. The effects of the agonists can be reversed by the respective antagonists of these receptors. Evidence is reviewed suggesting that the effect of endogenous 5-HT is mediated by 5-HT_{2A} receptors and the effect of endogenous dopamine by D_1-like receptors. Data are presented on the effects of lesions of the prefrontal cortex and corpus striatum on the sensitivity of performance on the FOPP to D_1-like and D_2-like receptor agonists. Lesions of the nucleus accumbens, but not the dorsal striatum or prefrontal cortex, attenuated the effects of a D_1-like receptor agonist, 6-chloro-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine [SKF-81297], but not a D_2-like receptor agonist, quinpirole, on T_{50}. The results indicate that a population of D_1-like receptors in the ventral striatum may contribute to the control of timing performance on the FOPP.

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1. Introduction

Many types of reinforcement schedule have been devised to assess interval timing in animals. According to the taxonomy proposed by Killeen and Fetterman (1988), these may be grouped into three main classes based on the relationship between the animal's timing response and the interval being timed. These classes are (i) *retrospective* timing schedules, in which the subject is trained to emit different responses depending on the duration of an interval that has already elapsed when the response is made (temporal discrimination), (ii) *immediate* timing schedules, in which the subject's behaviour comes under the control of time during an ongoing interval (temporal differentiation), and (iii) *prospective* timing schedules, in which the animal is trained to emit discriminative responses on the basis of intervals that follow the responses (inter-temporal choice).

Although the phenomena of interval timing revealed by different types of timing schedule have many features in common (Gibbon, 1977, 1991; Ho et al., 2002; Killeen and Fetterman, 1988; Killeen et al., 1997), there is evidence that the indices of timing derived from different schedules display different patterns of pharmacological sensitivity (Asgari et al., 2005, 2006; Body et al., 2005; Chiang et al., 2000a,b; Hampson et al., 2010; see Section 3 for further discussion). The focus of this paper is the pharmacology of performance on one immediate timing schedule, the free-operant psychophysical procedure (FOPP) (Bizo and White, 1994a,b; Stubbs, 1976, 1980). Section 1.1 summarizes the basic phenomena of performance on the FOPP, and Sections 1.2 and 1.3 review data collected in the authors' laboratory on the sensitivity of performance on this schedule to drugs acting at 5-hydroxytryptamine (5-HT) and dopamine receptors. In Section 2, two experiments are described which examined the effects of lesions of the prefrontal cortex and corpus striatum on the sensitivity of performance on the FOPP to D_1-like and D_2-like

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dopamine receptor agonists. In Section 3, the relationship between findings obtained with the FOPP and extant data obtained with other types of timing schedule are discussed, and some possible implications of these findings for a general account of the biological bases of interval timing are considered.

1.1. The free-operant psychophysical procedure (FOPP)

In this procedure each experimental session consist of a series of trials in which reinforcement is provided, usually on a variable-interval schedule, for responding on two continuously available operanda (Stubbs, 1976, 1980). Reinforcement availability is allocated to operandum A during the first half and to operandum B during the second half of each trial. The typical pattern of responding on the FOPP consists of increasing response rate on operandum B and concomitantly declining response rate on operandum A during the course of the trial. This is reflected in an increasing relative response rate on operandum B, $\%B$ (i.e. response rate on operandum B divided by the combined response rate on both operanda), which passes the indifference point (50% responding on operandum B) approximately midway through the trial (see below). The relationship between relative response rate and time measured from the onset of the trial is well described by the same logistic function that has been found to define the psychometric curve in many other timing tasks (Bizo and White, 1994a,b; Chiang et al., 1998; Killeen et al., 1997; Stubbs, 1976, 1980). The principal indices of temporal differentiation derived from the psychometric curve are the indifference time, T_{50}, a measure of the central tendency of temporal differentiation defined as the time at which $\%B = 50$, and the Weber fraction, a measure of the precision of temporal differentiation, defined as the ratio of the limen to T_{50}, the limen being defined as half the difference between the times at which $\%B = 75\%$ and $\%B = 25\%$.

Conventionally, timing performance is assessed in a small proportion of the trials in which reinforcement is withheld (probe trials). This ensures that the indices of timing are not influenced by the discriminative effects of reinforcer delivery (Bizo and White, 1994a,b). In general it has been found that T_{50} derived from the standard variable-interval trials occurs close to the point in time when reinforcer availability is transferred from operandum A to operandum B (Bizo and White, 1997; Stubbs, 1976, 1980). However, T_{50} derived from the probe trials generally occurs somewhat earlier within the trial (Bizo and White, 1997; Chiang et al., 1998).

In the original version of the FOPP, the subject is able to switch back and forth between the two operanda throughout the trial ('unconstrained switching') (Stubbs, 1976, 1980), whereas more recent studies have generally incorporated a contingency that prevents repetitive switching ('constrained switching'). Chiang et al. (1998, 1999) compared two versions of the FOPP, one in which switching was unconstrained and the other in which it was restricted to one switch per trial by withdrawal of operandum A after the first response on operandum B. The psychometric function was steeper and the Weber fraction smaller in the latter version of the FOPP than in the former. In rats trained to steady state under the constrained-switching condition, removal of the constraint had no significant effect on T_{50} (Chiang et al., 1998). However, subsequent studies comparing the performance of rats trained under the two versions of the FOPP have generally found somewhat shorter indifference times in the constrained-switching version of the schedule (Chiang et al., 2000a,b).

Al-Zahrani et al. (1996) found that destruction of the ascending 5-HTergic pathways resulted in substantially enhanced switching rate in the unconstrained-switching version of the FOPP, and predicted that this increase in the propensity to switch between operanda would result in premature switching, and hence a reduction of T_{50}, in the constrained-switching version of the FOPP (see also Al-Ruwaitea et al., 1997, 1999; Ho et al., 1998). However, this proved not to be the case; the parameters of temporal differentiation have generally been found to be unaffected by destruction of the 5-HTergic pathways (Chiang et al., 1999; Body et al., 2001, 2002). It seems, therefore, that although the constraint on switching is associated with some reduction of T_{50}, switching and temporal differentiation are not entirely interdependent.

1.2. 5-Hydroxytryptamine receptors and performance on FOPP

There are at least 14 different subtypes of 5-HT receptor, all but one of which, the 5-HT_3 receptor, belong to the metabotropic (G-protein coupled) 'super-family' (Bockaert et al., 2010; Hannon and Hoyer, 2008). Various behavioural functions have been proposed for most of the 5-HT receptor subtypes (Barnes and Sharp, 1999; Pytliak et al., 2011; Hayes and Greenshaw, 2011). This section focuses on the 5-HT_{1A}, 5-HT_{2A} and 5-HT_3 receptors, which are the only subtypes whose potential role in interval timing has been examined in detail.

1.2.1. 5-HT_{1A} receptors

5-HT_{1A} receptors are expressed on the somata, dendrites and terminals of 5-HTergic neurones, where they are believed to serve a release-inhibitory function, and are also expressed post-synaptically on target neurones of the 5-HTergic projection (Barnes and Sharp, 1999; Hannon and Hoyer, 2008). The 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) induced a dose-dependent leftward displacement of the psychometric function in the FOPP, reducing T_{50} (Chiang et al., 2000b; Body et al., 2001, 2002, 2004). This effect could be antagonized by systemic treatment with the 5-HT_{1A} receptor antagonist N-[2-(4-[2-methoxyphenyl]-1-piperazinyl)ethyl]-N-2-pyridinylcyclohexanecarboxamide (WAY-100635). WAY-100635 itself had no effect on T_{50}, suggesting that 5-HT_{1A} receptors are not tonically active during performance on the FOPP (Body et al., 2002). The effect of 8-OH-DPAT appears to be mediated by a postsynaptic receptor population, because the effect of 8-OH-DPAT survived destruction of the 5-HTergic pathways by intra-raphe injection of the selective serotonergic neurotoxin 5,7-dihydroxytryptamine (5,7-DHT) (Body et al., 2002, 2004; Chiang et al., 1999).

1.2.2. 5-HT_{2A} receptors

5-HT_{2A} receptors are widely distributed in the central nervous system, and there is evidence that these receptors are responsible for several of 5-HT's behavioural roles (Barnes and Sharp, 1999). The 5-HT_{2A} receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) has been found to reduce T_{50} in the FOPP, an effect that could be antagonized by the 5-HT_{2A} receptor antagonists ketanserin (Body et al., 2003, 2005, 2006a) and (±)2,3-dimethoxyphenyl-1-(2-(4-piperidine)methanol) (MDL-100907) (Body et al., 2003, 2006a). The 5-HT releasing agent fenfluramine also reduced T_{50}, an effect that could be antagonized by ketanserin but not by WAY-100635, suggesting that 5-HT_{2A} receptors rather than 5-HT_{1A} receptors are mainly responsible for mediating fenfluramine's effect. Destruction of the 5-HTergic pathways by intra-raphe injection of 5,7-DHT abolished the effect of fenfluramine, but not that of DOI (Body et al., 2004). These findings suggest that the reduction of T_{50} by fenfluramine is brought about by an interaction of released 5-HT with a postsynaptic population of 5-HT_{2A} receptors. Destruction of the 5-HTergic pathways or administration of 5-HT_{2A} receptor antagonists had little or no effect on T_{50} (Chiang et al., 1999; Body et al., 2003, 2004, 2005,